PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4 -32544A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/10579	23.09.2003	24.09.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/135		
Applicant		
NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.03.2004	12.10.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Deck, A Telephone No. +49 89 2399-8432

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10579

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-26 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-13 (partially)

because:

☒ the said international application, or the said claims Nos. 6-10 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4, 6-8, 11-13 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	see separate sheet

2. Citations and explanations

see separate sheet

Concerning section III

3.1. Claims 6-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3.2. The international preliminary report is drawn for the first group of inventions mentioned in the search report and which has been the subject of the search, i.e. claims 1-13 partially: "Pharmaceutical compositions comprising a sphingosine-1-phosphate receptor agonist and a co-agent which is an interferon; uses thereof in the treatment of a demyelinating disease."

Concerning section V

1. The following documents are referred to; the numbering will be adhered to in the rest of the procedure:

D1: WO 02 18395 A (PARSONS WILLIAM H ;HAJDU RICHARD (US); BERGSTROM JAMES (US); CARD) 7 March 2002 (2002-03-07) cited in the application

D2: EP-A-1 002 792 (YOSHITOMI PHARMACEUTICAL) 24 May 2000 (2000-05-24) cited in the application

D3: WO 02 072019 A (PARKER SUEZANNE E ;VICAL INC (US); HORTON HOLLY M (US)) 19 September 2002 (2002-09-19)

D4: DE 197 39 693 A (SCHERING AG) 11 March 1999 (1999-03-11)

D5: BRINKMANN VOLKER ET AL: 'The immune modulator FTY720 targets sphingosine 1-phosphate receptors' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 24, 14 June 2002 (2002-06-14), pages 21453-21457, XP002264445 ISSN: 0021-9258

D6: BRINKMANN V ET AL: 'FTY720: targeting G-protein-coupled receptors for sphingosine 1-phosphate in transplantation and autoimmunity' CURRENT OPINION IN IMMUNOLOGY, CURRENT BIOLOGY LTD, XX, vol. 14, no. 5, 19 July 2002 (2002-07-19), pages 569-575, XP004377409 ISSN: 0952-7915

D7: MOSER HUGO W: 'Clinical and therapeutic aspects of adrenoleukodystrophy and adrenomyeloneuropathy' JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, vol. 54, no. 5,

1995, pages 740-745, XP009022840 ISSN: 0022-3069

D8: HOSHINO Y ET AL: 'FTY720, a novel immunsuppressant, shows a synergistic effect in combination with FK 506 in rat allograft models' TRANSPLANTATION PROCEEDINGS, vol. 31, no. 1-2, February 1999 (1999-02), pages 1224-1226, XP002264446 XVIIth World Congress of the Transplantation Society;Montreal, Quebec, Canada; July 12-17, 1998 ISSN: 0041-1345

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2. The documents D1 and D2 disclose the use of S1P receptor agonists in the treatment of autoimmune disorders e.g. multiple sclerosis. The S1P receptor agonist can be combined with a second immunosuppressive agent (see D1, page 13, line 27, and D2, page 19, line 34).

The documents D3 discloses the use of interferon beta in the treatment of inflammatory disorders, e.g. multiple sclerosis.

The document D4 further discloses the use of interferon beta in the treatment of multiple sclerosis in combination with a co-agent, e.g. prostacyclin.

D5 and D6 report that the S1P receptor agonist FTY720 is a potent therapeutic agent for human multiple sclerosis as it is shown to be active in the rat model of multiple sclerosis, EAE.

D7 teaches that beta interferon is a potent therapeutic agent for adrenoleukodystrophy which is a demyelinating disorder.

Finally, D8 reports that a synergy has been observed with the combination of FTY720 with tacrolismus (FK506) as immunosuppressive composition.

3. None of the available prior art discloses the combination of a S1P receptor agonist and an interferon in a pharmaceutical composition, hence the subject-matter of claims 1-13 is novel.

4. However the subject-matter of claims 1-13 is not considered as inventive as the applicant has not shown any unexpected technical effect with the combination of a

S1P agonist with a co-agent being interferon. The application lacks experimental data as well as scientific explanations as to why such a combination would be inventive over the use of the agents separately and alone. S1P receptor agonists are disclosed in the art for the treatment of multiple sclerosis, as well as interferons. The simple combination of a S1P receptor agonist chosen among the multitude of compounds disclosed in the description, with an interferon, does not need particular inventive skills.
In addition, the applicant has not shown any evidences that the claimed invention works at all, hence the claimed invention is not inventive.

5. For the assessment of the present claims 6-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.